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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 4
DISCUSSION 4
AUTHORS' CONCLUSIONS 5
REFERENCES 6
CHARACTERISTICS OF STUDIES 6
DATA AND ANALYSES 8
Analysis 1.1. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 1 Tender joints per patient. 9
Analysis 1.2. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 2 Swollen joints per patient. 9
Analysis 1.3. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 3 ESR. 9
Analysis 1.4. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 4 Radiolological damage - Patients with new/worse erosions. 10
Analysis 2.1. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts - Total. 10
Analysis 2.2. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals due to inefficacy. 11
Analysis 2.3. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 3 Withdrawals due to adverse reactions. 11
WHAT'S NEW 11
DECLARATIONS OF INTEREST 11
SOURCES OF SUPPORT 12
INDEX TERMS 12

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[Intervention Review]

Cyclophosphamide for treating rheumatoid arthritis

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ABSTRACT

Background

The use of immunosuppressive drugs for the treatment of RA has been advocated for decades. Cyclophosphamide is an antineoplastic agent widely used in the treatment of cancer patients. It is an alkylating drug, with a marked cytotoxic effect on mononuclear cells and other leukocytes.

Objectives

To assess the short-term effects of cyclophosphamide for the treatment of rheumatoid arthritis.

Search methods

We searched the Cochrane Musculoskeletal Group's Register, the Cochrane Controlled Trials Register (issue 3, 2000), MEDLINE and Embase up to and including August 2000. We also carried out a handsearch of the reference lists of the trials retrieved from the electronic search.

Selection criteria

All randomized controlled trials (RCTs) and controlled clinical trials (CCTs) comparing oral cyclophosphamide against placebo (or an active drug at a dosage considered to be ineffective) in patients with rheumatoid arthritis.

Data collection and analysis

Data abstraction was carried out independently by two reviewers. The same two reviewers using a validated checklist (Jadad 1996) assessed the methodological quality of the RCTs and CCTs. Rheumatoid arthritis outcome measures were extracted from the publications for baseline and end-of-study. The pooled analysis was performed using standardized mean differences (SMDs) for joint counts. Weighted mean differences (WMDs) were used for erythrocyte sedimentation rate (ESR). Toxicity was evaluated with pooled odds ratios for withdrawals. A chi-square test was used to assess heterogeneity among trials. Fixed effects models were used throughout.

Main results

A total of 70 patients were included in the pooled analysis of two trials, 31 receiving cyclophosphamide. A statistically significant benefit was observed for cyclophosphamide when compared to placebo for tender and swollen joint scores: SMDs were -0.57 and -0.59 respectively. The difference in ESR also favoured the active drug but did not reach statistical significance (-12 mm, 95%CI: -26 to 2.5). One trial reported the number of patients developing new or worse erosions: the OR for cyclophosphamide compared to placebo was 0.17 (95% CI: 0.05 to 0.57).

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Patients receiving placebo were six times more likely to discontinue treatment because of lack of efficacy than patients receiving cyclophosphamide. Withdrawals from adverse reactions were higher in the cyclophosphamide group (Odds ratio=2.9), although this difference was not statistically significant. Side effects from cyclophosphamide included hemorrhagic cystitis, nausea, vomiting, leucopenia, thrombocytopenia, alopecia, amenorrhea and herpes zoster infections.

Authors' conclusions

Cyclophosphamide appears to have a clinically and statistically significant benefit on the disease activity of patients with RA, similar to some disease modifying antirheumatic drugs (DMARDs) such as antimalarials or sulfasalazine, but lower than methotrexate. Toxicity however is severe, limiting its use given the low benefit-risk ratio compared to other antirheumatic agents.

PLAIN LANGUAGE SUMMARY

Cyclophosphamide for treating rheumatoid arthritis

This review included 31 patients taking cyclophosphamide and 39 patients taking placebo. Patients taking cyclophosphamide had improved tender and swollen joint scores. Patients receiving placebo were six times more likely to discontinue treatment because of lack of treatment effect than patients receiving cyclophosphamide. Withdrawals from adverse reactions were higher in the cyclophosphamide group. Side effects from cyclophosphamide included hemorrhagic cystitis, nausea, vomiting, leucopenia, thrombocytopenia, alopecia, amenorrhea and herpes zoster infections.

Cyclophosphamide appears to have a clinically and statistically significant benefit on the disease activity of patients with rheumatoid arthritis. But due to serious side effects, its use should remain limited to patients who have failed treatment with various other therapies.

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BACKGROUND

The use of immunosuppressive drugs for the treatment of RA has been advocated for decades. Cyclophosphamide is an antineoplastic agent widely used in the treatment of cancer patients. It is an alkylating drug, with a marked cytotoxic effect on mononuclear cells and other leukocytes. These effects result in suppression of immune responses thought to be involved in the pathogenesis of RA. The use of cyclophosphamide in patients with severe RA increased during the 1980's. The drug is generally perceived to be efficacious although its use has been limited to patients failing other therapies because of concerns over its toxicity as a cytotoxic agent. It is unclear however if the benefits of the drug in reducing disease activity are superior to those of other less toxic agents.

OBJECTIVES

To evaluate the short-term efficacy and toxicity of cyclophosphamide for the treatment of RA, by conducting a systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCT) comparing cyclophosphamide and placebo.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and controlled clinical trials (CCT) , with a minimum duration of the study of 6 months.

Types of participants

Patients with a diagnosis of RA (as stated in the publication)

Types of interventions

Intervention group: cyclophosphamide - minimum dosage > 75 mg/day or >1mg/kg/day, oral administration
Control group: placebo or active drug at a dosage considered to be ineffective.

Types of outcome measures

1. Efficacy

All the outcome measures in OMERACT (Outcome Measures for Rheumatoid Arthritis Clinical Trials 1993) were included for potential analysis, although only some were consistently reported across trials.

OMERACT measures for efficacy include:
a) Number of tender joints per patient
b) Number of swollen joints per patient
c) Pain
d) Physician global assessment
e) Patient global assessment
f) Functional status
g) Acute phase reactants
h) Radiological damage

2. Withdrawals and dropouts - these were analyzed as:

a) Total number of withdrawals and dropouts
b) Number of withdrawals from lack of efficacy
c) Number of withdrawals due to adverse reactions

Search methods for identification of studies

1. Electronic searches
We searched the Cochrane Musculoskeletal Group's Register, the Cochrane Controlled Trials Register (issue 3, 2000) and MEDLINE using the strategy developed by Dickersin (Dickersin 1994) up to and including August 2000, EMBASE was searched from 1988 to August 2000, with a strategy similar to the one used for MEDLINE,

2. Hand searches
Reference lists of all the trials selected through the electronic search were manually searched to identify additional trials.

Data collection and analysis

Data extracted from the publications included study characteristics and outcome measures of efficacy and toxicity. Data was extracted by one reviewer and cross checked by a second (EB, MS), using predetermined forms.

1. Efficacy

Only two trials could be evaluated for efficacy by meta-analysis of OMERACT outcome measures (Townes 1976, CCC 1970). Both trials reported three of the OMERACT measures: number of tender joints, number of swollen joints and ESR.

The two trials reported medians instead of means, and 80% ranges. We used end of trial medians as an estimate of end of trial means. The 80% range was divided by 2 to estimate the baseline standard deviation.

End-of-trial results were pooled as standardized weighted mean differences (SMD) for joint scores, using the pooled baseline standard deviation. This was necessary because of the potential variation in the outcome measures included in each study (e.g. different number of swollen joints). Trial results were entered in RevMan 3.0 using the same direction to enable the pooling of results where the lowest value was improvement and the highest value was worsening. ESR results were pooled using a weighted mean difference (WMD). Negative values in SMD and WMD indicate a benefit of the active drug over placebo.

Only one study included radiological assessments (CCC 1970). The results were analyzed comparing the number of patients with new or worsened erosions in the placebo and treatment groups.

2. Withdrawals and dropouts

Adverse reactions were generally reported as overall results at the end of the trial. We therefore pooled withdrawals and dropouts at the end of the study. Toxicity was analyzed using a pooled odds ratio for total withdrawals from adverse reactions.

The heterogeneity of the trials for each pooled analysis was estimated using a chi-square test.

Fixed effects models were used throughout since no statistically significant heterogeneity was observed.

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RESULTS

Description of studies

Six CCTs were originally considered for potential inclusion in the meta-analysis, but only 2 trials were finally included in the meta-analysis (CCC 1970, Townes 1976). One trial was excluded because it included mostly patients with connective tissue diseases other than RA (Fries 1970). Another trial was excluded because the treatment group received lower or borderline dosages than required by our inclusion criteria, and the data reported was incomplete for the analysis (Smyth 1975). Another study also used a low cyclophosphamide dose (Lidsky 1973). The last trial (Williams 1980) included two groups with one receiving 150 mg and the other 75 mg of cyclophosphamide with no control group on placebo.

Of the included trials, one had a cross-over design, and only the results of the first arm were included in the meta-analysis (Townes 1976). The duration of the trial was 8 months for the initial study (CCC 1970) and 9 months for the first arm of the second study (Townes 1976).

The control group in the CCC 1970 trial did not receive a placebo, they were treated with low doses of cyclophosphamide not exceeding 15 mg/day. We considered this dose to be low enough to evaluate this group as a control with no beneficial effects from cyclophosphamide.

These studies were conducted in patients with severe longstanding RA, who had failed therapy with previous DMARDS.

Risk of bias in included studies

The methodological quality of the studies was assessed by two of the investigators (EB, MS) using a quality scale validated and published by Jadad 1996. This scale includes an assessment of randomization, double-blinding procedures and description of withdrawals. The possible range of scores is 0 (worst) to 5 (best). One study had a score of 3 (CCC 1970) and the other a score of 4 (Townes 1976).

Effects of interventions

A total of 70 patients were included in the pooled analysis, 31 receiving cyclophosphamide. Cyclophosphamide was statistically significantly better than placebo when considering the joint indices. The SMD for the tender joint score was -0.57 (95%CI: -1.05; -0.09), for swollen joints -0.59 (95%CI: -1.08; -0.10). The WMD for ESR between treatment and placebo groups was -11.6 mm and did not reach statistical significance (95% CI -25.7, 2.5).

Although the results of global assessments were included in the trials, they could not be pooled because the data reported was inadequate for meta-analysis. One trial [CCT 1970] examined radiological scores. The measure reported here is based on the number of patients with new or worse erosions at the end of the study, and is reported as an OR. Statistically significant results favoured cyclophosphamide, (OR=0.17 - 95%CI: 0.05; 0.57).

No statistically significant differences were observed in the number of withdrawals and dropouts between the placebo and treatment groups (OR=0.79; 95%CI:0.27 - 2.26). Nevertheless, withdrawals due to lack of efficacy were only observed in the placebo groups (3/48 vs 0/40). Patients receiving cyclophosphamide were more likely to withdraw because of toxicity than controls, but the difference was not statistically significant (OR 2.9, 95%CI:0.54 - 10.0). The overall prevalence of cyclophosphamide toxicity (with or without withdrawal) was high. Odds ratios comparing treatment and control groups could not be estimated for most adverse reactions since many occurred only in the treatment groups. By combining the results of both trials (considering both arms of the Townes 1976 study), approximately 90% of the 43 patients included in this review receiving cyclophosphamide had one or more side effects. These included nausea and/or vomiting (58%), alopecia (26%), dysuria (26%), hemorrhagic cystitis (14%), herpes zoster (5%). Other adverse reactions included leucopenia, thrombocytopenia and amenorrhea in premenopausal women.

No statistically significant heterogeneity among trials was observed for any of the outcome measures.

DISCUSSION

Cytotoxic agents were initially used for the treatment of RA in the early 1950's (Diaz 1951, Scherbel 1957). Cyclophosphamide, an alkylating agent with cytotoxic and immunosuppressive properties was initially used in patients with RA by Fosdick (Fosdick 1968). Controlled clinical trials in the 1970's suggested that cyclophosphamide was superior to placebo and that it could be used for patients with severe, aggressive disease, non responsive to other agents (CCC 1970).

The purpose of this systematic review was to evaluate the efficacy and toxicity of cyclophosphamide for the treatment of patients with RA, when compared to placebo. We only included in this review placebo-controlled RCTs and CCTs, reporting results after at least 6 months of treatment. The minimum dosage of cyclophosphamide required was 75mg/day or 1 mg/kg/day. This dosage was chosen because the benefit from lower dosages is uncertain (Lidsky 1973). Only two trials complied with our inclusion criteria. Several others could not be included in the systematic review: two of these evaluated insufficient dosages (Lidsky 1973, Smyth 1975), one included patients with various connective tissue diseases (Fries 1970), and the last study compared two dosages of cyclophosphamide without an additional control group (Williams 1980).

Overall, only 70 patients, 31 on cyclophosphamide, could be included in the pooled analysis of efficacy. Statistically significant results favouring the active treatment were observed for tender and swollen joint scores. The magnitude of the effect was approximately 0.5 to 0.6, which can be considered as moderate. This is comparable to the results found in meta analyses of some other disease modifying agents used for the treatment of RA such as antimalarials or sulfasalazine, but lower than the efficacy observed with methotrexate, when compared to the results of meta-analyses using the same methodology (Cochrane Database of Systematic Reviews, Musculoskeletal Review Group).

These two trials were published before the publication of OMERACT and the American College of Rheumatology (ACR) core set of measures for RA (OMERACT 1993, Felson 1993) and the CONSORT approach (Begg 1996).

Some of the measures recommended by OMERACT and the ACR, such as functional status or pain were not included in the trials. Although global assessments had been measured, data reporting

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did not allow for meaningful pooling of the results. The available measures, joint counts and ESR, were reported as medians and 80% ranges. We estimated means and standard deviations from these values. Although these procedures may have created some bias, we believe that their impact is small because they were similarly applied to both groups (treatment and control).

The CCC 1970 trial [CCC 1970 1970] included a radiological evaluation, which showed a marked protective effect from cyclophosphamide, with significantly more patients in the placebo group developing new or worse erosions. These results however, were based on 48 patients and have not been replicated by others.

Toxicity from cyclophosphamide was frequent and severe. Although only 6 of the 40 patients receiving cyclophosphamide included in the meta-analysis withdrew because of adverse reactions, side effects were severe, including hemorrhagic cystitis, herpes zoster and leucopenia. In one trial [CCC 1970 1970], one third of the patients on 150mg of cyclophosphamide experienced hair loss and half of them nausea and vomiting.

One of the trials [Townes 1976 1976] had a cross-over design with two 9-month arms. After cross-over to placebo, many patients experienced an increase in disease severity, evident after 3 months. This suggests that this drug does not induce prolonged remission and has to be maintained over long periods of time. Given the drug's serious toxicity (hemorrhagic cystitis, leucopenia, infections) and its effects on quality of life (nausea, vomiting, hair loss) long term administration is not advisable. Furthermore, the risk of subsequent malignancies also has to be considered.

The two trials included in this review were conducted in the early 1970's. Since then, very few trials have evaluated the use of cyclophosphamide in RA, and have focused on the comparison of dosages or its use in combination with other antirheumatic drugs (Walters 1988). Despite the limited evidence of its benefit and its serious toxicity, cyclophosphamide has been extensively used to treat patients with 'refractory' RA unresponsive to other therapies. The available evidence suggests that its effect is not greater than that of other less toxic antirheumatic therapies, although the populations included in these two trials had severe arthritis, perhaps less responsive than those studied in trials of other drugs. Methotrexate nevertheless, appears to have a stronger effect with a safer toxicity profile.

AUTHORS' CONCLUSIONS

Implications for practice

Cyclophosphamide appears to be an effective drug for the treatment of RA, but its use is very limited because of its serious toxicity profile. Given that its efficacy appears to be similar to that of other less toxic antirheumatic drugs, its use should remain limited to patients who have failed treatment with various other therapies.

Implications for research

Although cyclophosphamide appears to be efficacious in the treatment of patients with RA, this evidence is based in few studies of small sample size. Nevertheless, because of its substantial toxicity, it does not appear to deserve further study. Efforts in this area should be directed to explore newer cytotoxic agents, which can perhaps offer similar efficacy with lower toxicity than cyclophosphamide.

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Lidsky 1973 *{published data only}*

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Additional references

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CCC 1970

Methods	Randomized allocation Double blind allocation Assessment not entirely blind Patients on low dose cyclophosphamide included as controls Sample size at entry:

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CCC 1970 *(Continued)*

	cyclophosphamide - 27 control - 37 Sample size analyzed cyclophosphamide - 20 control - 28
Participants	Patients with definite or classical active RA Median age: Tx - 55 yr; Controls - 48 yr Median duration of disease - Tx - 7 yr; Controls - 6 yr (all >=2 yr duration) Prevalence of RF - unknown No concomittant use of other DMARDS Concomitant use of steroids allowed Previous use of DMARDS - 100%
Interventions	Cyclophosphamide - 50 to 150mg/day Control group received cyclophosphamide 5 to 15mg/day Treatment duration - 32 weeks
Outcomes	OMERACT: Tender joints Swollen joints ESR Radiological scores OTHER: Grip strength Morning stiffness 50-foot walk
Notes	Quality score: 2 No intent to treat analysis Differences in medians used instead of differences in means Standard deviations estimated from ranges Global assessments measured but not reported as means or medians (only counts for higher scores)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Townes 1976

Methods	Randomized allocation Double blind allocation and assessment Cross-over study - only first arm (9 months included in review) Sample size at entry: cyclophosphamide - 13 placebo - 11 Sample size analyzed: cyclophosphamide - 11 placebo - 11
Participants	Patients with active severe classic RA Median age - Tx 52 yr - Placebo 55 yr Females - 63%

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Townes 1976 *(Continued)*

	Median duration of disease Tx 10 yr - Placebo 13 yr (at least 2 yrs) Prevalence of RF - 92% No concomitant use of other DMARDS Concomitant use of steroids allowed if <10mg/d Previous use of DMARDS - 100%
Interventions	Cyclophosphamide - 2-3.5 mg/kg/day (mean 1.85 mg/kg/day) Treatment duration - 9 months
Outcomes	OMERACT: Tender joints Swollen joints ESR OTHER: Grip strength Morning stiffness 50-foot walk
Notes	Quality score: 3 No intent to treat analysis Differences in medians used instead of differences in means Standard deviations estimated from baseline ranges Global assessments measured but not reported as means or medians (only counts for each score)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fries 1970	Patients with connective tissue diseases other than rheumatoid arhritis
Lidsky 1973	Low dosages of cyclophosphamide (50 to 70 mg/day) One-year study including 22 patients randomly assigned to cyclophosphamide or placebo. No statistically significant benefit from cyclophosphamide observed
Smyth 1975	No end of trial or baseline data reported, only before and after differences Low/borderline dosage of cyclophosphamide (75 mg/day) The trial included 29 patients (13 received cyclophosphamide). The results showed a statistically significant difference favouring patients on cyclophosphamide
Williams 1980	No placebo-controlled group; 2 treatment groups receiving cyclophosphamide at dosages of 75 mg/day and 150 mg/day respectively

DATA AND ANALYSES

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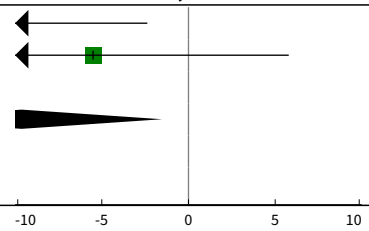
Comparison 1. Cyclophosphamide vs. placebo - Efficacy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tender joints per patient	2	70	Mean Difference (IV, Fixed, 95% CI)	-9.62 [-17.72, -1.53]
2 Swollen joints per patient	2	70	Mean Difference (IV, Fixed, 95% CI)	-6.88 [-12.04, -1.71]
3 ESR	2	70	Mean Difference (IV, Fixed, 95% CI)	-11.61 [-25.72, 2.51]
4 Radiolological damage - Patients with new/worse erosions	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.05, 0.57]

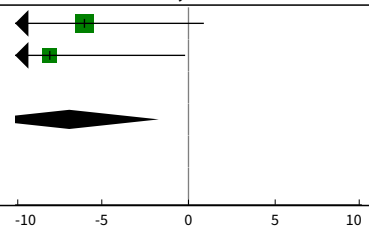
Analysis 1.1. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 1 Tender joints per patient.

Study or subgroup	Cyclophosphamide N	Cyclophosphamide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CCC 1970	20	7 (18.5)	28	21 (22.5)		48.5%	-14[-25.63,-2.37]
Townes 1976	11	16.5 (13.5)	11	22 (13.5)		51.5%	-5.5[-16.78,5.78]
Total ***	**31**		**39**			**100%**	**-9.62[-17.72,-1.53]**
Heterogeneity: Tau^2=0; Chi^2=1.06, df=1(P=0.3); I^2=5.43%							
Test for overall effect: Z=2.33(P=0.02)							



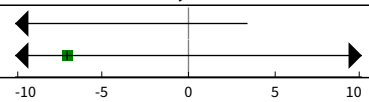
Analysis 1.2. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 2 Swollen joints per patient.

Study or subgroup	Cyclophosphamide N	Cyclophosphamide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CCC 1970	20	12 (12)	28	18 (12)		56.24%	-6[-12.89,0.89]
Townes 1976	11	3 (6.5)	11	11 (11.5)		43.76%	-8[-15.81,-0.19]
Total ***	**31**		**39**			**100%**	**-6.88[-12.04,-1.71]**
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%							
Test for overall effect: Z=2.61(P=0.01)							



Analysis 1.3. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 3 ESR.

Study or subgroup	Cyclophosphamide N	Cyclophosphamide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
CCC 1970	20	30 (26.5)	28	44 (35)		65.79%	-14[-31.41,3.41]
Townes 1976	11	42 (31.5)	11	49 (26)		34.21%	-7[-31.14,17.14]



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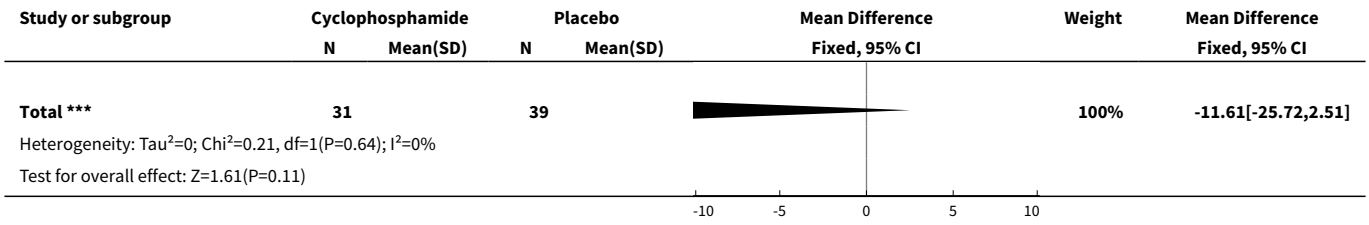
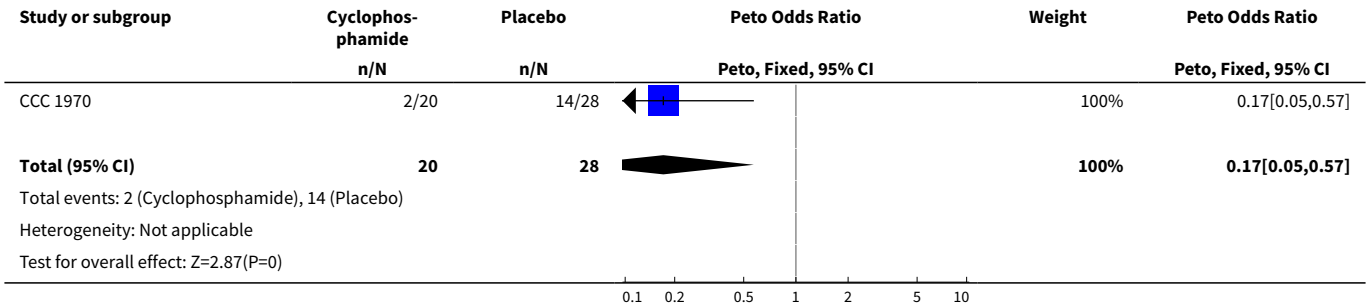


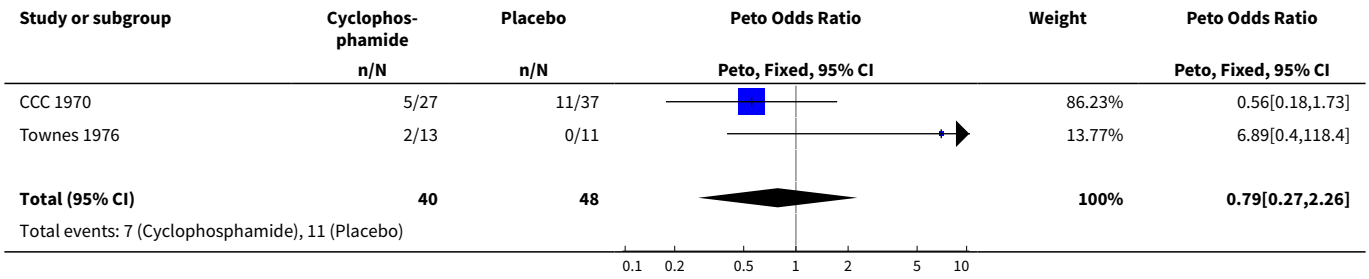
Analysis 1.4. Comparison 1 Cyclophosphamide vs. placebo - Efficacy, Outcome 4 Radiolological damage - Patients with new/worse erosions.



Comparison 2. Cyclophosphamide vs. placebo - Withdrawals and dropouts

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Withdrawals and dropouts - Total	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.27, 2.26]
2 Withdrawals due to inefficacy	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.02, 1.72]
3 Withdrawals due to adverse reactions	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.86 [0.71, 11.50]

Analysis 2.1. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 1 Withdrawals and dropouts - Total.



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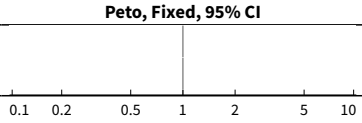
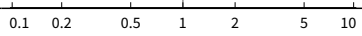
Study or subgroup	Cyclophos-phamide n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.6, df=1(P=0.11); I²=61.51%					
Test for overall effect: Z=0.45(P=0.65)					



Analysis 2.2. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 2 Withdrawals due to inefficacy.

Study or subgroup	Cyclophos-phamide n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
CCC 1970	0/27	3/37		100%	0.17[0.02,1.72]
Townes 1976	0/13	0/11			Not estimable
Total (95% CI)	**40**	**48**		**100%**	**0.17[0.02,1.72]**
Total events: 0 (Cyclophosphamide), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.5(P=0.13)					



Analysis 2.3. Comparison 2 Cyclophosphamide vs. placebo - Withdrawals and dropouts, Outcome 3 Withdrawals due to adverse reactions.

Study or subgroup	Cyclophos-phamide n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
CCC 1970	5/27	3/37		87.48%	2.55[0.58,11.3]
Townes 1976	1/13	0/11		12.52%	6.34[0.12,323.68]
Total (95% CI)	**40**	**48**		**100%**	**2.86[0.71,11.5]**
Total events: 6 (Cyclophosphamide), 3 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.18, df=1(P=0.67); I²=0%					
Test for overall effect: Z=1.48(P=0.14)					

WHAT'S NEW

Date	Event	Description
22 September 2008	Amended	Converted to new review format. C023-R

DECLARATIONS OF INTEREST

None known

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Internal sources

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Controlled Clinical Trials as Topic; Cyclophosphamide [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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